

Hemodynamic Interactions of Verapamil and Isoflurane

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The hemodynamic interactions of verapamil and isoflurane were studied in eight dogs. Left ventricular function was analyzed using a right heart bypass preparation to permit rigid hemodynamic control. Hemodynamic studies were performed at 0.7, 1.05, and 1.40% isoflurane before and during the maintenance of two stable levels of verapamil, administered intravenously by combining a bolus dose ($0.2 \text{ mg} \cdot \text{kg}^{-1}$) with an infusion (3.0 and $6.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Isoflurane produced a concentration-dependent depression of left ventricular function as indicated by dP/dt max, per cent systolic shortening, and left ventricular function curves. This depression was enhanced in a dose-plasma concentration-dependent manner by verapamil and was reversed by calcium chloride. Isoflurane alone and the combination of verapamil and isoflurane decreased systemic vascular resistance in a dose-dependent fashion that was antagonized partially by calcium chloride. Therefore, verapamil can enhance the hemodynamic effects of isoflurane in a dose-related manner that needs to be considered when both drugs are administered together. (Key words: Anesthetics, volatile; isoflurane. Heart: myocardial function. Hemodynamics: systemic vascular resistance. Ions: calcium. Pharmacology: verapamil, calcium chloride.)

VERAPAMIL IS a calcium-channel-blocking drug that affects cardiac conduction, contractility, and vascular smooth muscle tone. Isolated tissue preparations have shown that the drug has negative chronotropic, dromotropic, and inotropic actions; however, in the intact animal, marked systemic vasodilation can result in improvement in cardiac output.^{1,2} In humans, the cardiovascular effects of verapamil are influenced by the patient's hemodynamic condition, disease state, and concurrent drug therapy.^{3,4}

Isoflurane, like other halogenated inhalational anesthetics, depresses myocardial contractility and vascular smooth-muscle tone in isolated tissue preparations.^{5,6} A dose-related depression of ventricular function in the intact dog also has been demonstrated.⁷ This direct cardiac depressant effect has been shown to be attenuated

by a reduction in systemic vascular resistance because of the vasodilating properties of isoflurane.⁷

This study was designed to evaluate the hemodynamic interactions of verapamil and isoflurane in the dog. Because previous studies have demonstrated the effects that heart rate, preload, and afterload have upon cardiac performance, a canine right heart bypass preparation was studied in order to permit rigid control of these hemodynamic variables.

Methods

Studies were performed with eight mongrel dogs weighing $24.4 \pm 2.4 \text{ kg}$. Anesthesia was induced with thiopental ($18 \text{ mg} \cdot \text{kg}^{-1}$) plus succinylcholine ($1 \text{ mg} \cdot \text{kg}^{-1}$ bolus, followed by an infusion of $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ throughout the study). The trachea was intubated and the dogs received 100% oxygen via a constant volume, positive-pressure ventilator set to maintain the PaCO_2 at 35–40 mmHg. Maintenance of anesthesia was provided by isoflurane 1.40% (1 MAC) during establishment of the right heart bypass preparation.

The heart was exposed via a median sternotomy and suspended in a pericardial cradle. Right heart bypass was established by cannulating the right atrium, inferior vena cava and right iliac vein for venous return, the main pulmonary artery to control pulmonary artery inflow, and the thoracic aorta (via the left subclavian artery) and iliac artery for systemic arterial inflow. A Spiraflor Bos-10® bubble oxygenator (Bentley Laboratories) was primed with 2 l of fresh heparinized dog blood from a donor animal and 1 l of Macrodex® 6% w/v (Pharmacia Laboratories). The animals were heparinized and treated with diphenhydramine ($5 \text{ mg} \cdot \text{kg}^{-1}$) to avoid the sequelae of transfusion reactions from the donor blood. Heart rate was controlled by crushing the sinoatrial node and instituting atrioventricular sequential pacing at a rate of $150 \text{ beats} \cdot \text{min}^{-1}$ with a P-R interval of 0.10 s using an A-V® sequential pulse generator (Medtronic, Inc., #5330).

After cannulation, the animals were connected to the extracorporeal right heart bypass circulation. Blood withdrawn from the venous cannulae was passed through the oxygenator and pumped back into the main pulmonary artery. In addition, blood was infused or withdrawn through the aortic and iliac arterial cannulae in order to maintain the mean systemic pressure at 100 mmHg. Pulmonary ventilation was discontinued and isoflurane was administered by a Forane® vaporizer

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(Ohio Medical Products, Inc.) that was incorporated into the oxygenator-gas inflow circuit. The esophageal temperature was maintained at 37–38° by adjustment of water bath temperatures in the heat exchanger of the oxygenator. The hematocrit was kept between 25 and 30% by addition of donor red blood cells to the cardiotomy reservoir. Arterial blood gas determinations were performed at 15-minute intervals and oxygenator gas flow adjusted to maintain Pa_O₂ > 100 mmHg and Pa_{CO}₂ 35–40 mmHg. If metabolic acidosis developed, it was treated with sodium bicarbonate (84 ± 43 mEq/animal mean ± SD) before measuring hemodynamic variables in order to maintain serum pH 7.35–7.40.

The experiment was designed to expose the canine cardiovascular system to stepwise increases in isoflurane before and during the maintenance of two stable levels of verapamil in plasma. Three series of left ventricular function studies were performed: 1) control, before verapamil administration; 2) during low-dose verapamil administration; and, 3) during high-dose verapamil. Low-dose verapamil consisted of a bolus dose of 0.2 mg · kg⁻¹ and a constant infusion of 3.0 μg · kg⁻¹ · min⁻¹, and high dose was achieved by a repeat bolus of 0.2 mg · kg⁻¹ and a constant infusion of 6.0 μg · kg⁻¹ · min⁻¹. Cardiovascular variables during verapamil administration were not studied until at least 15 min after initiating the intravenous infusion. Before each series, the animal also was stabilized for 15 min after reaching the appropriate isoflurane level (0.70, 1.05, 1.40, and 0.70%). The nonrandomized sequence of isoflurane levels always was accompanied by a final return to initial levels. Isoflurane concentrations were measured continuously during right heart bypass at the one-way exhaust valve of the oxygenator by a Beckman LB-2 infrared gas analyzer. Verapamil concentrations in serum obtained at 15-min intervals were analyzed using high-pressure liquid chromatography analysis (Bioscience Laboratories, Bellwood, Illinois). Good reproducibility has been demonstrated with this technique (average coefficient of variation, 3.7%).⁸

Femoral arterial and left atrial pressures were measured using Hewlett-Packard (Model 12904) quartz pressure transducers zeroed to the level of the tricuspid valve. Left ventricular pressure and the first derivative of left ventricular pressure (dP/dt) were monitored using a Mikrotip[®] catheter pressure transducer (Millar Instruments) inserted via the left carotid artery across the aortic valve.

Regional myocardial function was estimated using a multichannel sonomicrometer (Schussler and Associates). A pair of myocardial cord length sonomicrometer crystals were placed in the midventricular wall of the left ventricle approximately 1.5 cm apart and perpendicular to the long axis of the left ventricle. The method

has been described previously.⁹ Measured end-systolic and end-diastolic cord lengths enabled the magnitude of systolic shortening to be calculated. Regional left ventricular dimensions were measured using the instant of the initial upstroke of the left ventricular pressure as the moment of end-diastole, and 20 ms prior to the maximum negative dP/dt as the moment of end-systole. Percentage of systolic shortening was determined to be the difference between the cord lengths measured at end-diastole and end-systole and was calculated by the formula:

$$\frac{(\text{End-diastolic length} - \text{End-systolic length}) \times 100}{\text{End-diastolic length}}$$

The right heart bypass preparation was used for analysis of left ventricular function. The pulmonary artery cannula occlusively was snared into the right ventricular outflow tract, and pulmonary blood flow provided by the calibrated roller pump determined left ventricular output. Calibrated roller pump flow rates were varied to achieve left ventricular outputs of 500–4,000 ml · min⁻¹. Left atrial pressure, left ventricular pressure, maximum left ventricular dP/dt (dP/dt max), and myocardial cord length were measured in response to incremental increases in cardiac output. Left ventricular function curves were constructed by plotting the change in left atrial pressure at each increment of cardiac output. During the generation of each set of ventricular function curves, percentage of systolic shortening and dP/dt max were evaluated when the left atrial pressure equaled 10 mmHg. Systemic vascular resistance was calculated at each level of cardiac output. When left atrial pressure is constant, the amount of blood ejected by the left ventricle is equal to the amount of blood pumped into the pulmonary artery. Therefore, the roller pump flows are a measure of total systemic blood flow, and because the mean aortic pressure was maintained at 100 mmHg and the right atrial pressure was 0 mmHg in this preparation, the systemic vascular resistance (SVR) could be calculated as:

$$\frac{(100 \text{ mmHg} - 0 \text{ mmHg}) \times 80}{\text{Combined calibrated forward roller pump flow}}$$

For all animals, the statistical mean SVR was determined from flow rate measurements at each cardiac output level during each isoflurane concentration, before and during each of the constant infusions of verapamil.

In order to determine the effectiveness of calcium chloride in antagonizing the combined actions of isoflurane and verapamil, a final set of hemodynamic measurements were made 1 minute after a calcium chloride bolus dose (20.7 ± 2.2 mg · kg⁻¹) during exposure to 0.70% isoflurane and the high infusion rate of verapamil.

TABLE 1. Serum Verapamil Levels ($\text{ng} \cdot \text{ml}^{-1}$)

	Time after Bolus and Infusion Begun				Mean for entire infusion period
	15 min	30 min	45 min	60 min	
Low Dose	36.6 ± 3	33.9 ± 2	34.7 ± 2	35.2 ± 3	35.1 ± 2
High Dose	76.2 ± 5	66.9 ± 4	66.2 ± 4	70.0 ± 4	70.5 ± 4

The data were evaluated by analysis of variance, and studentized multiple tests¹⁰ for comparisons between individual pairs of mean values. The effect of calcium chloride was evaluated by Student's paired *t* test. Significance was defined as $P < 0.05$. All values in the text, tables, and figures are given as the mean \pm SEM.

Results

The canine right heart bypass preparation allowed us to maintain rigid control of hemodynamic variables. For the eight dogs, both the heart rates and mean aortic

pressures nearly were identical (150 ± 0 beats \cdot min⁻¹, 100 ± 2 mmHg, respectively) and constant throughout each study. Each of the desired isoflurane concentrations was maintained with minimal variation during the 15-minute equilibration period and the subsequent hemodynamic measurement period. Verapamil serum levels did not differ significantly among the samples taken at 15-minute intervals during each infusion. Low-dose verapamil resulted in mean serum levels of 35.1 ± 2 ng \cdot ml⁻¹ and high dose, 70.5 ± 4 ng \cdot ml⁻¹. (table 1).

Frank-Starling relationships were plotted, with left atrial pressure (LAP) as a function of cardiac output (CO); that is, *decreased* myocardial performance is evident as an *increase* in the slope indicating a higher LAP for a given cardiac output, (fig. 1). Evaluation of linear regression lines derived from each set of data points revealed that isoflurane produced a significant concentration-dependent increase in the LAP/CO slope ($P < 0.05$). When the isoflurane concentration was decreased from 1.40–0.70%, the slope decreased and was not significantly different from that calculated for the initial measurements at 0.70% isoflurane (not shown). The addition of verapamil produced a further dose-dependent increase in the LAP/CO slope (*i.e.*, increasing degrees of depression) for all concentrations of isoflurane ($P < 0.05$). The pattern of the concentration-dependent depression with isoflurane was maintained ($P < 0.05$) at both levels of verapamil. When the isoflurane concentration was decreased to 0.70% during continued exposure to verapamil, the LAP/CO slope decreased significantly but did not recover completely to the slope determined initially for the lowest concentration of isoflurane in the presence of verapamil (not shown). The antagonism of calcium chloride to the combined effects of verapamil and isoflurane was evident as a significant decrease in the slope ($P < 0.05$, not shown).

Isoflurane decreased dP/dt max in a concentration-dependent manner ($P < 0.0001$, fig. 2). A decrease in isoflurane concentration from 1.40–0.7% resulted in an increase in dP/dt max to a level not significantly different from that measured during the initial exposure to 0.70% isoflurane alone. This depression was enhanced in a dose-plasma concentration-dependent manner by verapamil ($P < 0.005$ among the groups), while the concentration-dependent effect of isoflurane still was evident at each verapamil dose ($P < 0.0001$ within

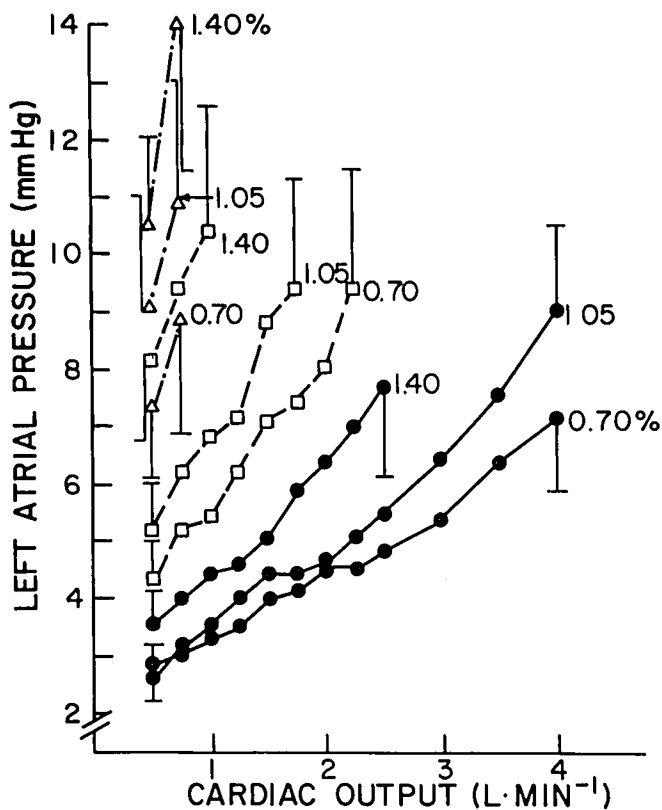


FIG. 1. Left ventricular function curves relating left atrial pressure and cardiac output. Ventricular depression is reflected by an increase in slope. Pooled linear regression analysis of each set of data points revealed that as isoflurane concentration increased (0.70%, 1.05%, 1.40%), the slope significantly increased ($P < 0.05$). Verapamil further increased the slope in a dose-dependent fashion ($P < 0.05$). Control (●—●—●), verapamil low dose (□—□—□), verapamil high dose (Δ—Δ—Δ).

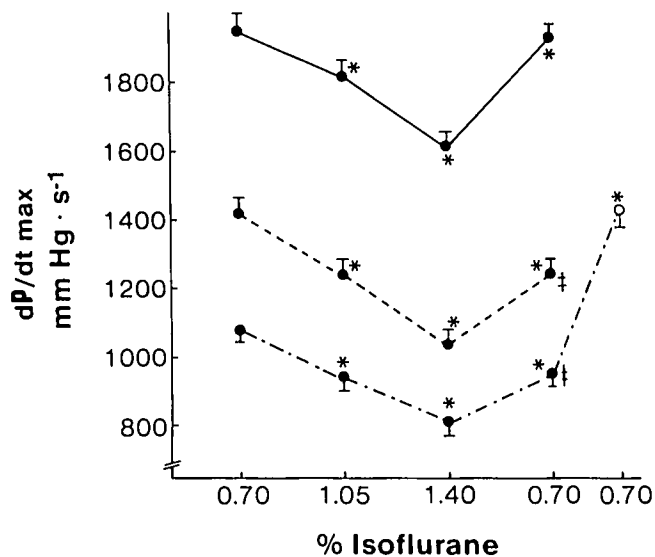


FIG. 2. Left ventricular dP/dt max measured at a constant left atrial pressure (10 mmHg). A dose-dependent depression by isoflurane is shown ($P < 0.0001$). The depression is enhanced in a dose-plasma concentration-dependent manner by verapamil ($P < 0.005$). Calcium chloride increased dP/dt ($P < 0.05$). Control (—●—), verapamil low dose (---○---), verapamil high dose (-·-·-●-·-·-), CaCl₂(○). *Statistical difference from previous data point ($P < 0.05$). †Statistical difference between initial 0.70 and final 0.70% isoflurane for each verapamil level ($P < 0.05$). (Symbols apply to all figures.)

each group). With the return to the lowest concentration of isoflurane during continued exposure to verapamil, dP/dt max improved significantly but did not recover to the value measured during the initial exposure to 0.7% isoflurane at the same verapamil level.

Regional wall motion similarly was affected by the combination of the two drugs (fig. 3). The decrease in percentage of systolic shortening by isoflurane ($P < 0.005$) was enhanced in a dose-dependent fashion by verapamil ($P < 0.0001$). The administration of calcium chloride significantly antagonized the combined depression of verapamil and isoflurane as determined by all indices of left ventricular function ($P < 0.05$).

Isoflurane alone decreased systemic vascular resistance in a concentration-dependent fashion (fig. 4, $P < 0.05$). The addition of verapamil further decreased systemic vascular resistance in a dose-dependent manner ($P < 0.001$). However, increasing isoflurane concentrations during verapamil administration did not alter systemic vascular resistance significantly in a concentration-related manner. Calcium chloride significantly increased systemic vascular resistance in the presence of both isoflurane and verapamil ($P < 0.05$).

The acute effects of verapamil on systemic vascular resistance were determined during the first 15 minutes after beginning its administration (fig. 5). Resistance decreased rapidly to its lowest level by 2.5 minutes (P

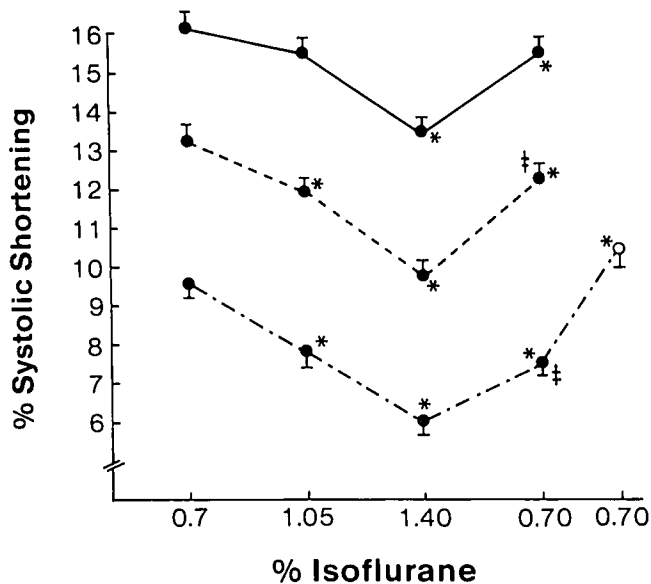


FIG. 3. Percentage systolic shortening measured at a constant left atrial pressure (10 mmHg). The dose-dependent effects of isoflurane ($P < 0.005$) are enhanced by verapamil ($P < 0.0001$). Calcium chloride increased systolic shortening ($P < 0.05$). (Symbols defined in figure 2.)

< 0.001 for the low dose and $P < 0.005$ for the high dose) and then gradually returned toward control values. There was no significant difference in the systemic

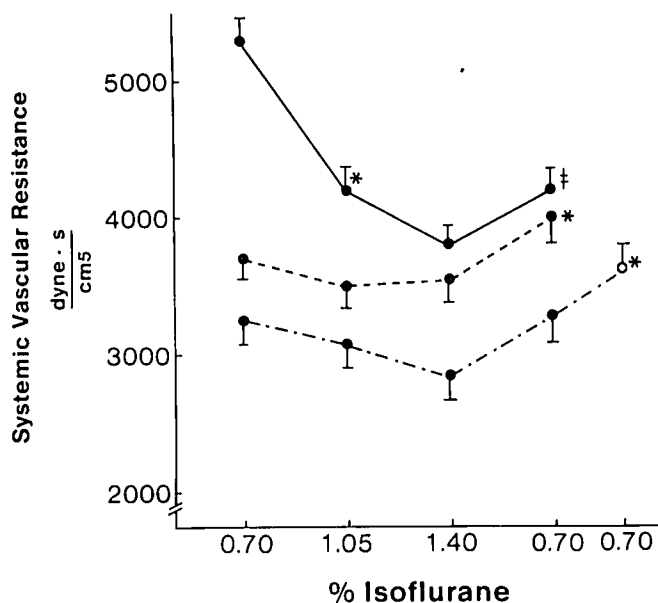


FIG. 4. Systemic vascular resistance was decreased by isoflurane in a dose-dependent manner before verapamil ($P < 0.05$). Verapamil caused a further dose-dependent decrease ($P < 0.001$). Changes in isoflurane levels during verapamil administration did not cause a statistically significant dose-related change in systemic vascular resistance. Calcium chloride increased systemic vascular resistance ($P < 0.05$). (Symbols defined in figure 2.)

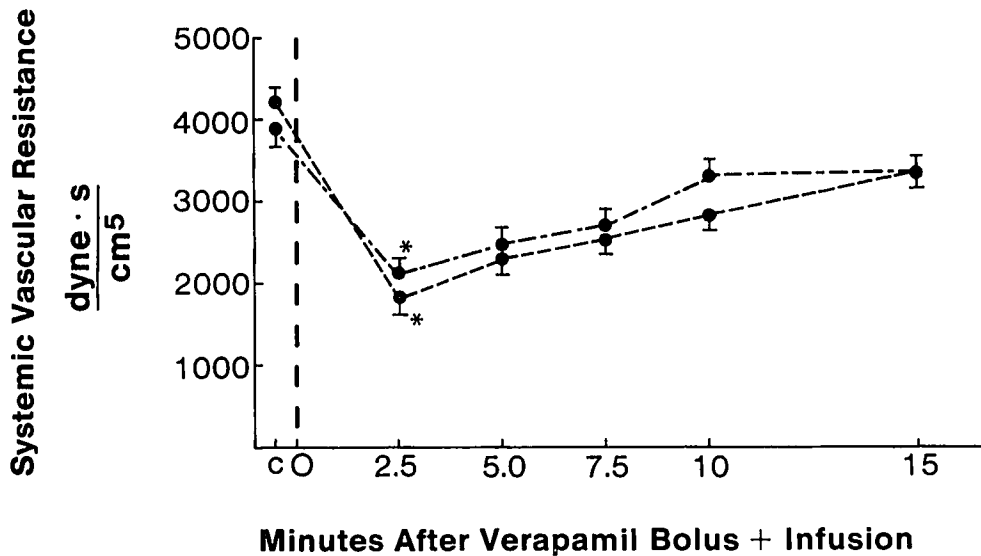


FIG. 5. Systemic vascular resistance during isoflurane (0.70%) anesthesia and during the first 15 min verapamil administration. Both the low (---) and high dose (- · - · -) verapamil significantly decreased the systemic vascular resistance ($P < 0.001$ and $P < 0.005$, respectively). The maximum decrease in resistance occurred at 2.5 min ($P < 0.05$ from control). At the 10 and 15 min measurement for both high- and low-dose verapamil (respectively), systemic vascular resistance was recovered significantly ($P < 0.05$ from 2.5 min). (Symbols defined in figure 2.)

vascular resistance at the low and high levels of verapamil.

Discussion

The primary purpose of this study was to determine the effects of isoflurane alone and the combined effects of isoflurane and verapamil on cardiovascular function. The canine right heart bypass model was chosen because it allowed rigid control of hemodynamic variables. By maintaining a constant mean aortic blood pressure, systemic vasodilatation leading to decreased vascular resistance and afterload could not mask depression of cardiac performance. Sequential A-V pacing was used to prevent changes in rate and rhythm that can affect left ventricular function. This highly controlled preparation permitted us to study left ventricular performance and systemic vascular tone but did not allow us to evaluate the chronotropic or dromotropic effects of the drugs.

The use of blood from another dog to prime the extracorporeal circuit necessitated pretreatment of the animals with diphenhydramine, an antihistamine selective for H_1 -receptors. This should not have modified the effects of verapamil or isoflurane on cardiac function because histamine receptors in the heart predominantly are of the H_2 -type.¹¹ Also, the only significant hemodynamic effect reported for diphenhydramine (in humans) was a mild increase in heart rate, a variable controlled successfully by cardiac pacing in this study.¹²

To evaluate the negative inotropic effects of verapamil administration during isoflurane anesthesia, ventricular function was studied during both the isovolumic and ejection phases of systole. Maximum left ventricular dP/dt occurred before the aortic valve opened and provided an indirect measure of contraction velocity during

the isovolumic phase of mechanical systole.¹³ Because heart rate, preload, and afterload were constant in our study, dP/dt max provided a reliable and sensitive measure of contractility.^{14,15} Ventricular function curves relating changes in left atrial pressure to cardiac output and determinations of the magnitude of systolic shortening of myocardial cord lengths were used to evaluate the ejection phase of systole, or pump function.¹⁶

All three indices of left ventricular performance demonstrated a direct, dose-related depression of left ventricular function by isoflurane in the dog. This is compatible with previous studies. In isolated cat papillary muscle, the maximum velocity of shortening, as well as other indices of contractility, were decreased by isoflurane in a dose-dependent manner.⁵ Studies in the intact dog anesthetized with isoflurane also revealed a dose-dependent depression in left ventricular function.⁷

Verapamil causes a direct negative inotropic effect resulting from selective blockade of calcium influx across myocardial cell membranes.¹⁷ Its myocardial depressant properties have been demonstrated in the isolated heart.¹ In the intact dog, measurements of cardiac output and maximum left ventricular dP/dt revealed dose-dependent myocardial depression by verapamil.²

The interaction between verapamil and inhalational anesthetic agents has been studied in the intact dog. Bolus doses of verapamil administered during halothane anesthesia resulted in a dose-dependent, transient depression of myocardial function.¹⁸ However, simultaneous changes in cardiac rhythm, preload, and afterload make it difficult to assess the effects of the combination of verapamil and isoflurane on cardiac function *per se*. In studies of isoflurane⁷ and of verapamil during halothane anesthesia,¹⁸ there were drug-induced reductions in systemic vascular resistance that attenuated

the direct negative inotropic effects. This allowed for a greater hemodynamic tolerance of verapamil and isoflurane in these previous animal studies than was evident in our right heart bypass preparation. Because our experimental model maintained a constant mean aortic pressure in the presence of increasing doses of verapamil and isoflurane, relatively low doses of these drugs resulted in substantial myocardial depression. The direct negative inotropic effects unrelieved by afterload reduction limited the dose range of isoflurane to a maximum of 1.0 MAC (1.4% isoflurane).

In our study, the administration of verapamil during isoflurane anesthesia resulted in greater depression of cardiac function than that resulting from isoflurane alone. The degree of additional myocardial depression by verapamil was dependent on the dose and plasma concentration of this calcium channel blocker. At each of two steady plasma concentrations of verapamil, the dose-dependent myocardial depression of isoflurane could be demonstrated. When isoflurane levels were reduced during verapamil administration, left ventricular function significantly improved but remained below control levels. Although plasma levels of verapamil remained constant, it is possible that there was a progressive increase in the tissue levels and in the negative inotropic effect of verapamil. Calcium chloride, an antagonist of the myocardial depressant effects of verapamil,¹⁹ and also of halothane,²⁰ reduced the combined negative inotropic effects of verapamil and isoflurane.

Systemic vascular resistance (SVR) was decreased by isoflurane in a concentration-dependent fashion. Bolus doses of verapamil administered during exposure to a constant level of isoflurane resulted in a prompt decrease in peripheral vascular resistance that was pronounced initially but tended to recover despite the continuous infusion of verapamil (fig. 5). The pronounced early decrease in SVR probably reflected the effects of initially high plasma (and tissue) levels of verapamil produced by the bolus dose and is in agreement with previous studies.^{18,21} The lesser effects sustained by lower plasma levels maintained by the infusion revealed a dose-plasma concentration-dependent reduction in SVR (fig. 4). However, in contrast to the heart, systemic vascular resistance did not show isoflurane-concentration-dependent changes during verapamil administration. The ability of calcium chloride to increase vascular smooth muscle tone²² still was present during the combined administration of verapamil and isoflurane.

Verapamil also causes a dose-related decrease in an A-V nodal conduction rate.²³ This negative dromotropic effect from verapamil is evident during halothane anesthesia.¹⁸ Although sequential pacing prevented any change in cardiac conduction in our study, it must be emphasized that when cardiac rhythm is not controlled,

conduction disturbances can affect left ventricular performance profoundly.

The possible extrapolations of our findings to the clinical situation are limited. However, these laboratory data demonstrate that verapamil enhances the hemodynamic effects of isoflurane in a dose-related manner that needs to be considered when both drugs are administered together in humans. The myocardial depressant effects of verapamil during isoflurane anesthesia can be reduced by decreasing the isoflurane concentrations and by administering calcium chloride.

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